Optimizing systemic insecticide use to improve malaria control

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Supplementary Text: Model development and calculations

1. Model development

Humans

$$\frac{dS_h}{dt} = r(E_h + I_h + A_h) + q_2 R_h - mb_h p_h S_h I_m \quad (1)$$

$$\frac{dE_h}{dt} = mb_h p_h S_h I_m - (\xi_h + r)E_h \quad (2)$$

$$\frac{dI_h}{dt} = \xi_h E_h - (q_1 + r)I_h \quad (3)$$

$$\frac{dR_h}{dt} = q_1(I_h + A_h) - (\theta mb_h p_h I_m + q_2)R_h \quad (4)$$

$$\frac{dA_h}{dt} = \theta mb_h p_h R_h I_m - (q_1 + r)A_h \quad (5)$$

$$b_h = a\, b\, (1 - C_N \frac{N^{Hn}}{N^{Hn} + LC_{50_N}[T_N]^{Hn}}) \quad (6)$$

Mosquitoes

$$\frac{dO}{dt} = \beta_{mc} V - d_o O - \mu_O \left(1 + \frac{O+L}{K}\right) O \quad (7)$$

$$\frac{dL}{dt} = d_O O - d_L L - \mu_L \left(1 + \gamma \frac{O+L}{K}\right) L \quad (8)$$

$$\frac{dP}{dt} = d_L L - d_P P - \mu_P P \quad (9)$$

$$\frac{dS_m}{dt} = \frac{1}{2} d_P P - b_m p_h (I_h + \sigma A_h) S_m - \mu_{mc} S_m \quad (10)$$

$$\frac{dE_m}{dt} = b_m p_h (I_h + \sigma A_h) S_m - (\xi_m + \mu_{mc}) E_m \quad (11)$$

$$\frac{dI_m}{dt} = \xi_m E_m - \mu_{mc} I_m \quad (12)$$

$$V = S_m + E_m + I_m \quad (13)$$

$$b_m = a\,c\,(1 - C_N \frac{N^{H_n}}{N^{H_n} + LC_{50_N}[T_N]^{H_n}}) \quad (14)$$

Insecticides

$$\frac{dD_L}{dt} = - k_{D_L} D_L \quad (15)$$

$$\frac{dD_H}{dt} = - k_{D_H} D_H \quad (16)$$

$$\frac{dN}{dt} = - k_N N \quad (17)$$

$$\beta_{mc} = \beta_m - \frac{1}{3}\left((1 - p_h) C_L \frac{D_L^{H_b}}{D_L^{H_b} + F_{50}{}^{H_b}} + p_h C_H \frac{D_H^{H_b}}{D_H^{H_b} + F_{50}{}^{H_b}}\right)\beta_m \quad (18)$$

$$\mu_{mc} = \mu_m + \frac{1}{3}\left(\begin{array}{c} p_h C_N \frac{N^{H_n}}{N^{H_n} + LC_{50_N}[T_N]^{H_n}} \mu_N + \\ (1 - p_h) C_L \frac{D_L^{H_d}}{D_L^{H_d} + LC_{50_D}[T_D]^{H_d}} \mu_D + \\ p_h C_H \frac{D_H^{H_d}}{D_H^{H_d} + LC_{50_D}[T_D]^{H_d}} \mu_D \end{array}\right) \quad (19)$$

$$\mu_N = \frac{2\log(2)}{T_N} \quad (20)$$

$$\mu_D = \frac{2\log(2)}{T_D} \quad (21)$$

Susceptible people are exposed (E_h) to malaria as a function of the proportion of bites that successfully leads to infection (b_m), the proportion of bites that are made on humans (p_h), the ratio of vectors to bloodmeal sources (m), and the number of infected mosquitoes (I_m). The transmission potential from vector to human or vice versa (b_h and b_m, respectively) is a function of biting frequency (a), the proportion of bites that successfully leads to infection in humans or mosquitoes (b and c, respectively), the coverage of bed nets (C_N) and whether the LLIN's insecticidal concentration is above the lethal dose for 50% ($LC_{50_N}[T_N]$) of the population. Exposed humans can either recover to the susceptible state at rate r or transition to the infected

state (I_h) at the rate at which the parasite matures (ξ_h). Infected humans can recover to the susceptible state or form immunity (R_h) at rate q_1 that is temporary (waning at rate q_2) and partial (as determined by at rate θ). Asymptomatic (A_h) humans can recover to a susceptible state or return to the immune state. The net change of human populations was assumed to be negligible for the timeframe observed.

All mosquitoes (V), regardless of their infection status, lay β_{mc} eggs per day. Coverage of systematic insecticides in livestock (D_L) or humans (D_H) (C_L and C_H, respectively) will affect the egg natural laying rate (β_m) if the drug concentration is above the concentration associated with a 50% fecundity reduction (F_{50}). Eggs hatch into early larval instars (O) that either develop into late instars (L) at rate d_O or die at a rate μ_O. Late larval instars develop into pupae (P) at rate d_L and die at rate μ_L. The death rates of the instar larval stages are dependent on the density of early and late larval instars and the environmental larval carrying capacity (K). To capture the different density dependences, the late larval instars' death rate is modified by γ. Pupae develop into sensitive mosquitoes (S_m, 50% of pupae are assumed to be female) at a rate d_P and die at rate μ_P. Sensitive mosquitoes are exposed (E_m) to malaria as a function of biting frequency, the proportion of bites that successfully lead to infection (c), the proportion of bites on humans, the ratio of vectors to bloodmeal sources, and the number of infected humans (I_h and A_h). Biting an asymptomatically infected human has a lower likelihood of leading to infection and is adjusted by factor σ. Mosquitoes become infectious at the rate of parasite development (ξ_m). Mosquitoes die at a natural rate of μ_m, but the coverage of LLINs and systematic insecticides in livestock (D_L) or humans (D_H) (C_N, C_L, C_H, respectively) will affect this if the drug concentrations are above the lethal dose for killing 50% of the population in a set period of time ($LC_{50_N}[T_N]$ and $LC_{50_D}[T_D]$). When the mosquitoes are exposed to sufficiently high doses of drug, the maximum

death rates due to LLINs (μ_N) and insecticides (μ_D) are approached. N_{death} and D_{death} are dependent on the lethal concentration for killing 50% of exposed mosquitoes ($LC_{50_N}[T_N]$ and $LC_{50_D}[T_D]$), the maximum death rate observed due to the insecticide in LLINs or systemic insecticides (μ_N and μ_D, respectively), and the time window over which the LC_{50} was determined (T_N and T_D). The insecticide in the LLINs and systemic insecticides in the host degrade at rates k_N, k_{D_L},and k_{D_H}, respectively. Initial conditions of $S_h(0) = 0.96$, $E_h(0) = I_h(0) = R_h(0) = A_h(0) = O(0) = L(0) = P(0) = S_m(0) = E_m(0) = I_m(0) = 0.01$ were used for all simulations.

2. Calculating $LC_{50}[T]$ of permethrin

Most studies reporting the $LC_{50}[T]$ of permethrin in bednets use the WHO bioassay for determining resistance in mosquitoes. The bioassay protocol calls for 1 hour of exposure time, which is much longer than mosquitoes normally rest on a bed net (3-15 minutes)[1217]. As such, we used a study that observed the number of mosquitoes killed when exposed to a LLIN for 3 minutes via a cone test [18]. Based on the number of mosquitoes killed in 24 hours after this exposure, the death rate (μ) and concentration ($LC_{50}[T]$) associated with killing 50% of an exposed mosquito population (M) in 24 hours post-exposure was derived. The death rate is dependent on drug (D) concentration.

1. Assume mosquito population follows exponential decay

$$M(t) = M(0)e^{-kt} \text{ where } k = \mu\left(\frac{D}{D+LC_{50}}\right)$$

2. Solve for μ when $D = LC_{50}$ and $M(t) = \frac{M(0)}{2}$ and $t = 1$ day

$$\mu = \frac{2\ln(2)}{\mathrm{t}} = 1.386/day$$

3. Solve for LC_{50} , assuming $\mu = 1.386/day$ and using parameters from Omondi study: D = 2%, M(t) =0.7, M(0), and t = 1 day

$$LC_{50} = D\left(\frac{\mu t}{-\ln\left(\frac{0.9M(0)}{M(0)}\right)} - 1\right) = 2\left(\frac{1.386}{\ln\left(\frac{1}{0.3}\right)}\right) = 3.426\%$$

The hill coefficient associated with the permethrin concentration and mortality observed was determined by fitting data with a nonlinear model. See online supplementary **Figure 1g-h**.

Table 1: Parameter values and definitions

Parameter	Definition	Ref.
$a = 0.2$	Biting frequency [0.01 – 0.5 day^{-1}]	[1]
$b = 0.5$	Proportion of bites that produce infection in humans [0.2 – 0.5]	[1]
$c = 0.5$	Proportion of bites that produce infection in mosquitoes [0.5]	[1]
$d_O = 0.15$	Rate at which early larval instars mature into late larval instars [days^{-1}]	[2]
$d_L = 0.27$	Rate at which late larval instars mature into pupae [days^{-1}]	[2]
$d_P = 1.56$	Rate at which pupae mature into adult mosquitoes [days^{-1}]	[2]
$m = 10$	Ratio of mosquitoes to blood meal sources [0.5 - 40]	[1]
$p_H = 0{:}1$	Availability of humans to all available blood hosts	[3,4]
$q_1 = 1/200$	Rate of immunity acquisition [days^{-1}]	[5]
$q_2 = 1/1000$	Rate of immunity loss [days$_{-1}$]	[5]
$r = 0.01$	Rate of recovery [0.005 – 0.05 day^{-1}]	[1]
$\beta_m = 21.19$	Number of eggs a mosquito lays per day	[2]
$\theta = 0.5$	Level of reduced susceptibility to secondary infection	[5]
$\sigma = 0.25$	Adjustment factor for asymptomatic infection transmissibility to vector	[5]
$\mu_O = 0.034$	Death rate of early larval instars at low density [days^{-1}]	[2]
$\mu_L = 0.035$	Death rate of late larval instars at low density [days^{-1}]	[2]
$\gamma = 13.25$	Factor to correct for different density dependent death rate of late vs. early larval instars [unitless]	[2]
$\mu_P = 0.25$	Death rate of pupae [days^{-1}]	[2]
$\mu_m = 0.12$	Death rate of mosquitoes [0.05 - 0.5 day^{-1}]	[1]
$\xi_m = 1/10$	Rate of *P. falciparum* maturation, given that latent period for mosquitoes is 5 - 15 days [days^{-1}]	[1]
$\xi_h = 1/21$	Rate of *P. falciparum* maturation, given that latent period for humans 10 - 100 days [days^{-1}]	[1]
$F_{50} = 0{:}8.5$	Threshold systemic insecticide concentration for reducing fecundity by 50% [ng/mL]: $F_{50} = 3.6$ ng/mL for ivermectin	[9]

	$F_{50} = 1.1$ ng/mL for eprinomectin $F_{50} = 9.2$ ng/mL for doramectin $F_{50} = 478.4$ ng/mL for moxidectin $F_{50} = 0$ ng/mL for fluralaner, afoxolaner, and spinosad. A conservative estimate, since these values need to be measured	
$LC_{50_D}[T_D]$= 7:1180	LC_{50} of systemic insecticides for *Anopheles* observed over set time [ng/mL] $LC_{50}[9]$ = 7.4 ng/mL for ivermectin $LC_{50}[9]$ = 7.6 ng/mL for eprinomectin $LC_{50}[1]$ = 21.2 ng/mL for fluralaner $LC_{50}[9]$ = 30.6 ng/mL for doramectin $LC_{50}[1]$ = 66.8 ng/mL for afoxolaner $LC_{50}[5]$ = 461 ng/mL for spinosad $LC_{50}[9]$ = 1178 ng/mL for moxidectin	[9–11]
T_D= 1 : 9	Time over which systemic insecticide LC_{50}s were observed [days] T_D= 1 days for afoxolaner and fluralaner T_D= 5 days for spinosyn T_D= 9 days for doramectin, eprinomectin, ivermectin, and moxidectin	[9–11]
$LC_{50_N}[T_N]$ = 3.43	LD_{50} for permethrin resistant mosquitoes exposed to Olyset nets observed over set time [%] (0.08% for susceptible). Assuming 30% of mosquitoes are killed in 24 hours following 3-minute exposure to a new Olyset net (2% permethrin).	[12], see next section for calculation
T_N = 1	Time over which LC_{50} for permethrin was observed [days]	[12]
$H_b = 0{:}16$	Hill coefficient for systemic insecticides and fecundity [unitless]	[9]
$H_d = 1{:}8.5$	Hill coefficient for systemic insecticides and death rate [unitless]	[9–11]
H_n = 2	Hill coefficient for resistant mosquitoes and permethrin in LLINs (H_n= 4 for susceptible) [unitless]	[12]
C_N= 0:0.75	Coverage by bed nets (0:1) * max efficacy of new LLIN (0.75)	[5]
C_L= 0:1	Livestock coverage by systemic insecticides (0:1) * max efficacy of newly applied drug (1)	[5]
C_H = 0:1	Human coverage by systemic insecticides (0:1) * max efficacy of newly applied drug (1)	[5]
$k_N = \frac{\ln(2)}{1906}$	After 7 years, Olyset nets had an average concentration of 6.6 g/kg permethrin[14]. With an initial concentration of 20 g/kg[15], the half life is calculated to be 5.2 years or 1906 days.	[15,16]
$k_L; k_H$=0.01:10	Rate of degradation of insecticide in host based on half lives recorded from literature search [$days^{-1}$]	From systematic review
$K = 3$	Environmental larval carrying capacity. Ranges from 1:10+	varied

$Net = 2$	Concentration of permethrin in new Olyset net [%] (1000 mg/m^2 or 20 g/kg)	[15]
$Dose = 1{:}10^5$	Concentration of insecticide at start of treatment based on C_{max} measured from literature search [ng/mL]	From systematic review
$period_N = 1095$	Recommended time between replacement Olyset nets [days]	[15]
$period_D = 7{:}365$	Time between administering new dose of systemic insecticide [days]	varied

Table 2: Pharmacokinetic values for coverage simulations

	C_{max} (ng/mL)	Half-life (days)	LC_{50}[T] (ng/mL)	Host	Drug	Route
Details for human coverage	40.7	3.4	7.4	human	ivermectin	oral
	20.1	4.8	7.6	other (small)	eprinomectin	topical
	1075.1	12.2	21.2	other (small)	fluralaner	topical
	4.2	8.0	30.6	other (small)	doramectin	topical
	621.9	14.8	66.8	dog	afoxalaner	oral
	1550.0	11.3	461.0	dog	spinosad	oral
	2.8	1.4	1178.0	other (small)	moxidectin	oral
Details for livestock coverage	14.5	7.8	7.4	cattle	ivermectin	topical
	11.0	3.5	7.6	cattle	eprinomectin	topical
	1075.1	12.2	21.2	other (small)	fluralaner	topical
	16.0	4.2	30.6	cattle	doramectin	topical
	621.9	14.8	66.8	dog	afoxalaner	oral
	1550.0	11.3	461.0	dog	spinosad	oral
	2.6	7.2	1178.0	cattle	moxidectin	topical

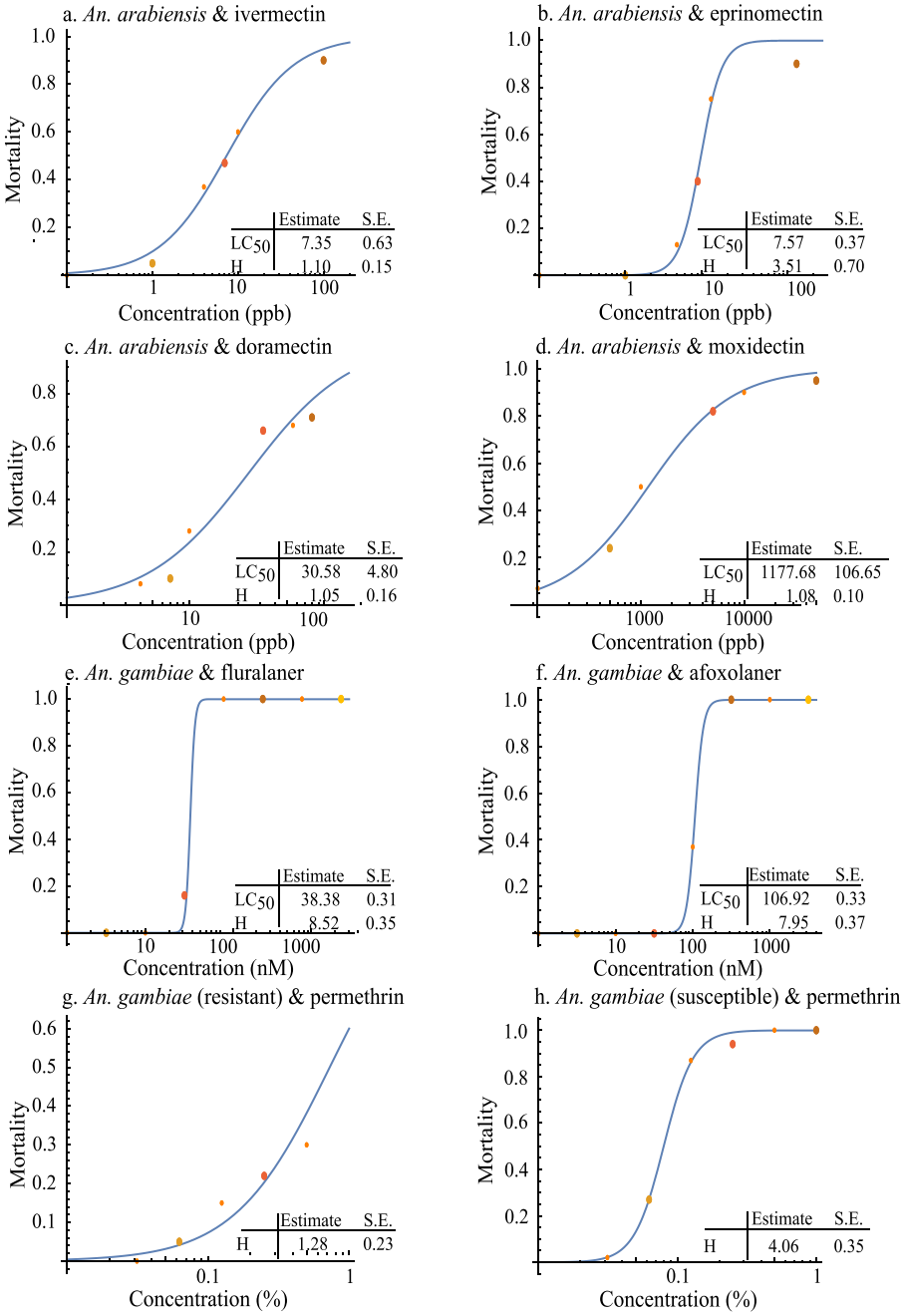

Figure 1. Estimating the hill coefficient (H) and LC_{50}[T]. **(a-h)** The mortality of mosquitoes for a range of concentrations was plotted for each systemic insecticide, recorded from [9,11,12]. Mathematica was then used to fit a nonlinear model to these data and estimate H and LC_{50}[T]. Please note that the LC_{50}[T] for permethrin was not calculated based on this data, due to the extended periods of exposure in the protocol. Please see previous section for calculations.

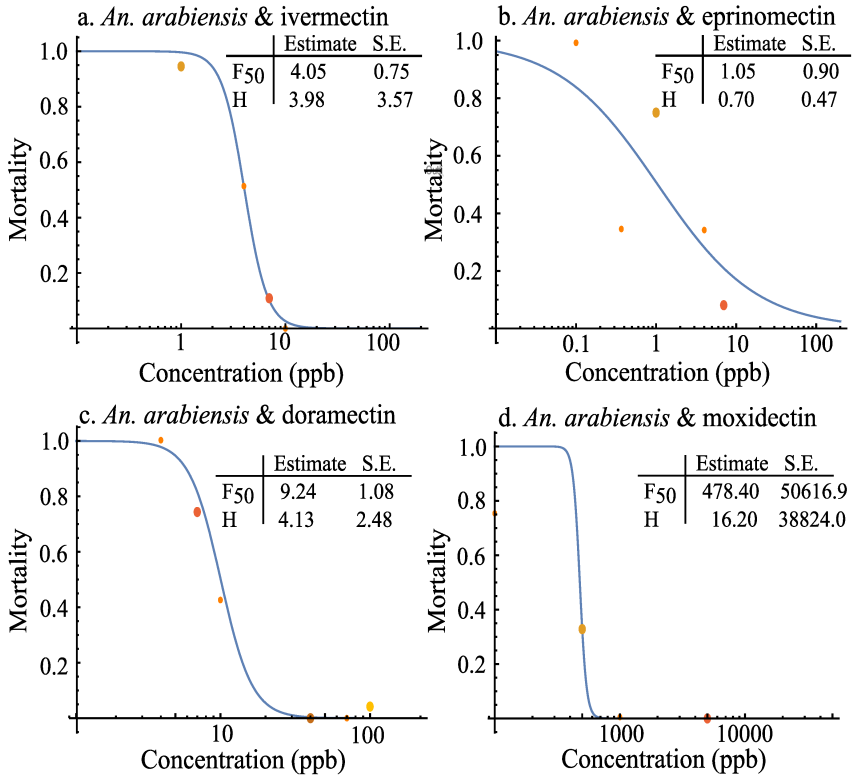

Figure 2. Estimating the hill coefficient (H) and concentration necessary to reduce number of eggs laid per day by 50% (F_{50}). **(a-d)** The mortality of mosquitoes for a range of concentrations was plotted for each systemic insecticide, recorded from [9]. A reduction in eggs laid per day has either not been observed or yet to be characterized for permethrin, the isoxazolines, and spinosad. Mathematica was used to fit a nonlinear model to these data and estimate H and F_{50}.

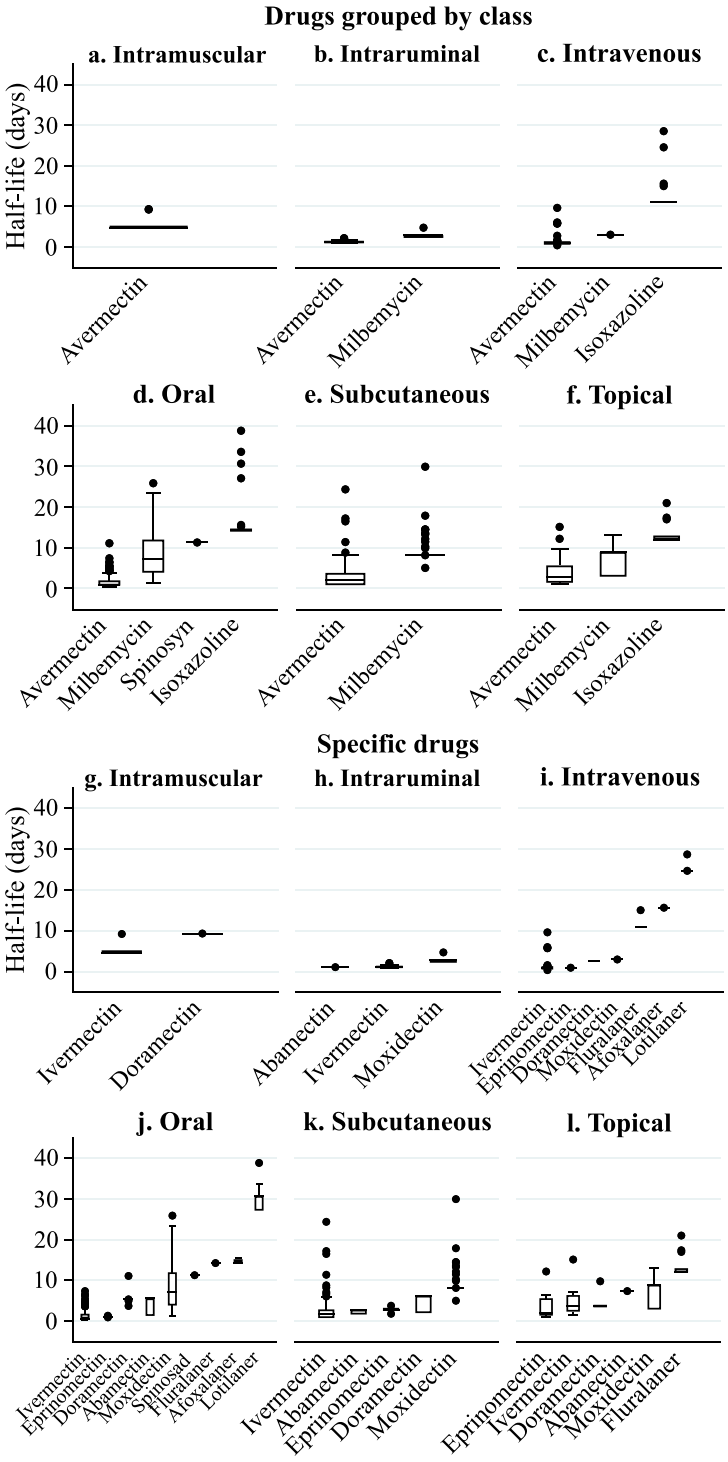

Figure 3. Interactions between route and drug on half-life. (**a-f**) Drugs are grouped into classes; (**g-l**) specific drugs are presented.

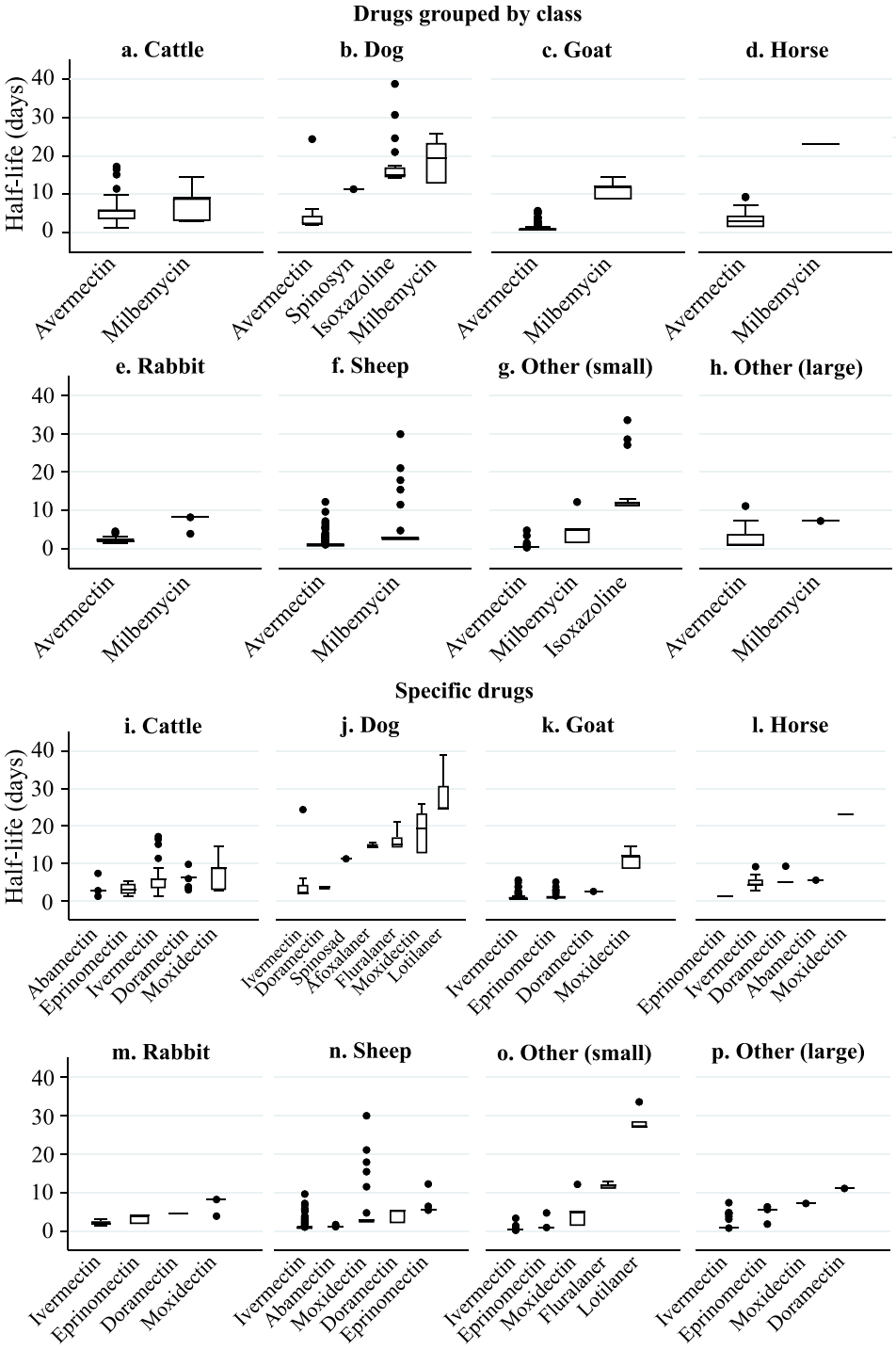

Figure 4. Effect of interactions between host and drug on half-life. (a-h) Drugs are grouped into classes; (i-p) specific drugs are presented.

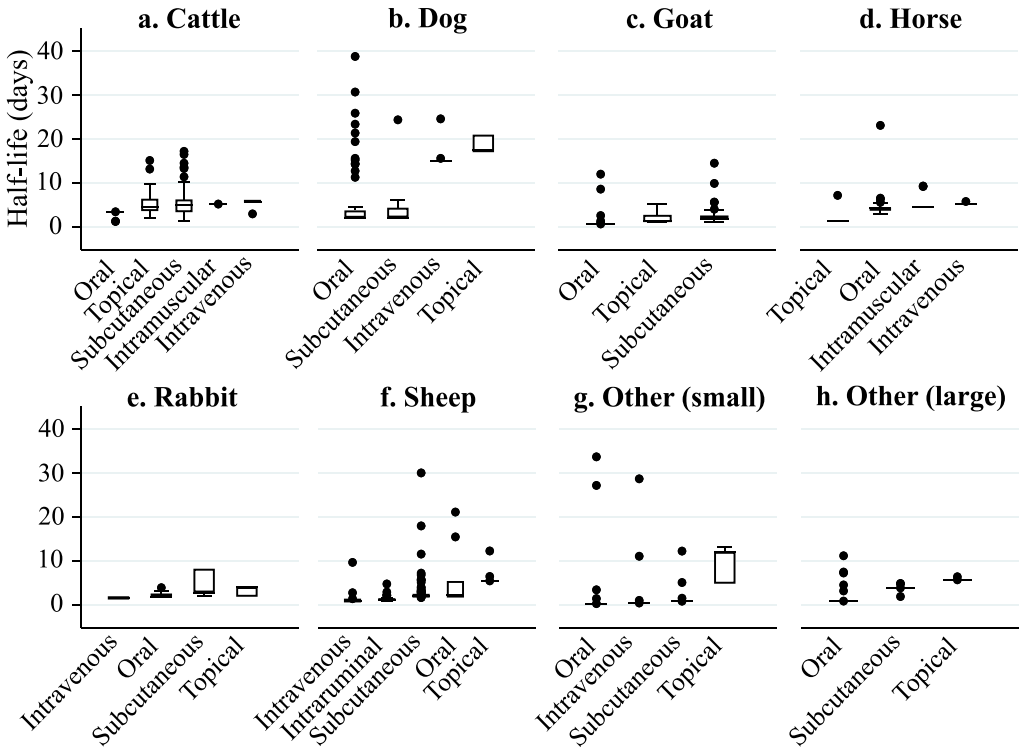

Figure 5. Effect of route and host on half-life.

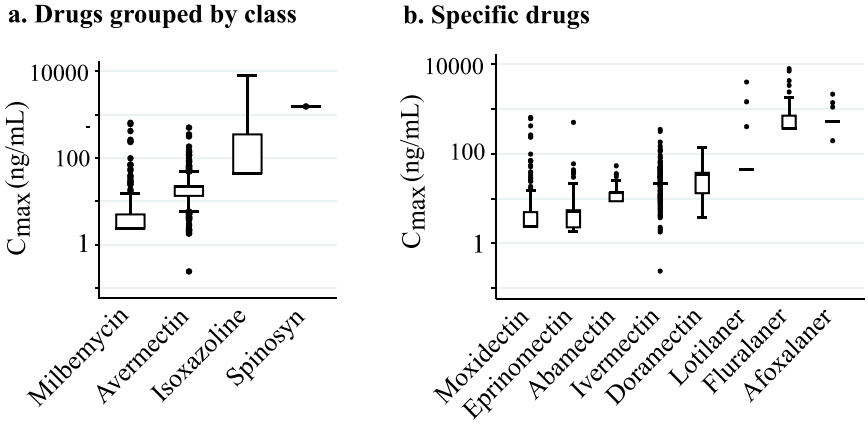

Figure 6. Effect of drug (a. class or b. specific) on $C_{max.}$

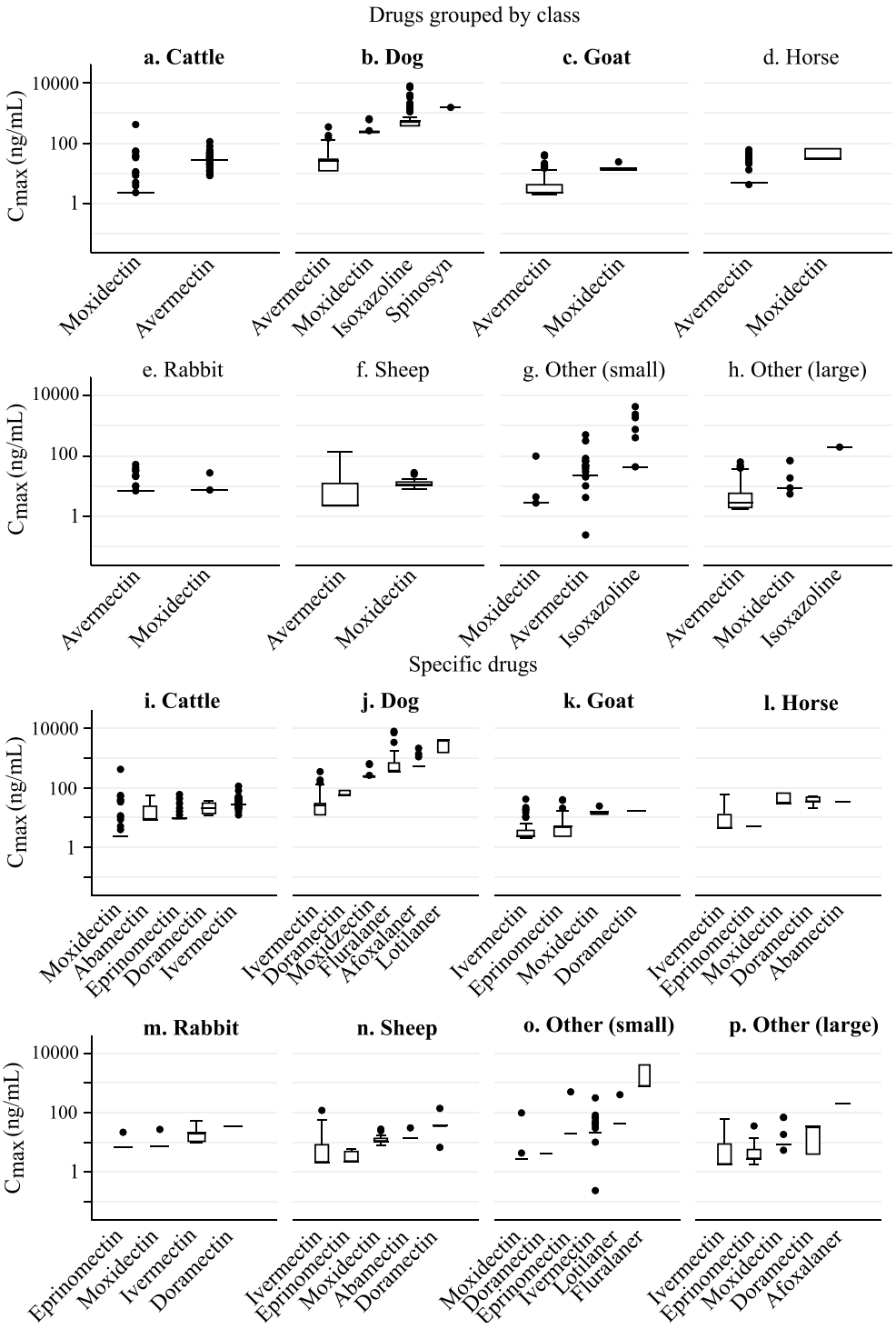

Figure 7. Effect of interactions between host and drug on C_{max}. (**a-h**) Drugs are grouped into classes; (**i-p**) specific drugs are presented.

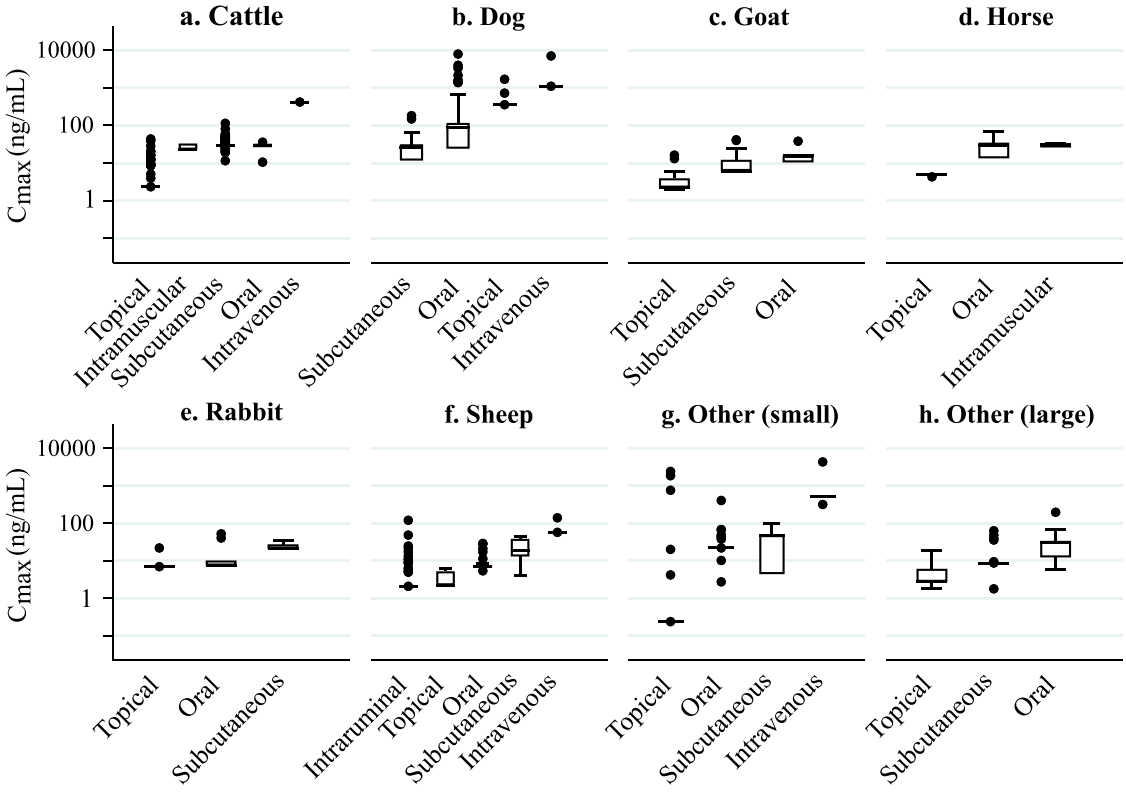

Figure 8. Effect of host and route on C_{max}

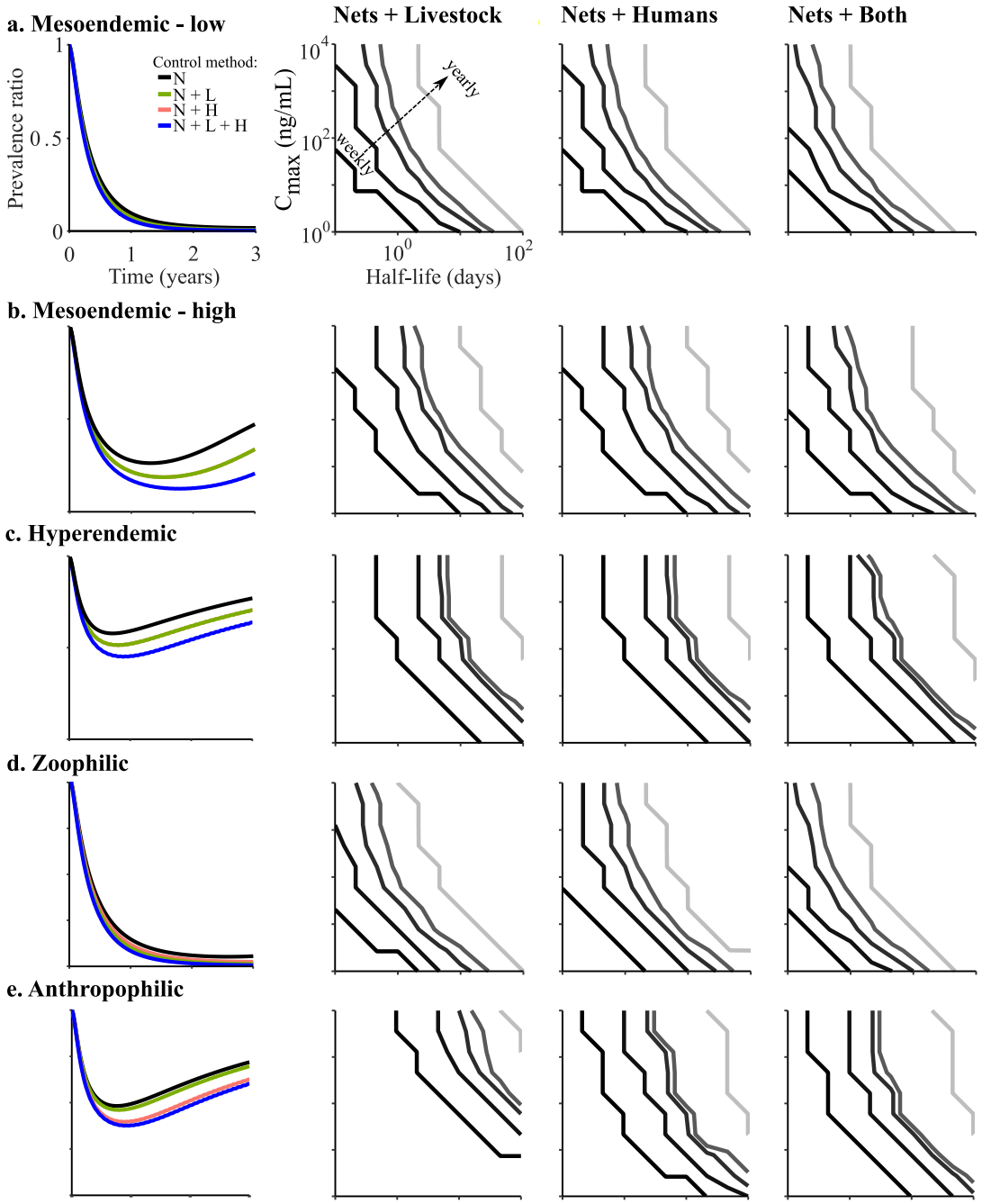

Figure 9 Effect of different coverage strategies using a drug similar to ivermectin in scenarios with different malaria prevalence classes and mosquito biting behaviours. The first column compares temporal dynamics of malaria prevalence for the different scenarios: LLINs alone (N), LLINs and livestock treatment (N+L), LLINs and human treatment (N+H), LLINs with both hosts treated (N + both). The three right columns are the predictions for dosing frequency

necessary to reduce malaria prevalence by 10% for each scenario. **(a-c)** With increasing malaria presence, the degree to which control methods can reduce malaria prevalence decreases and the frequency of insecticide reapplication increases (mesoendemic-low: m = 5; mesoendemic-high: m = 10; hyperendemic: m=20). Here, an indiscriminate biting behaviour is assumed in mosquitoes ($p_H = 0.5$), thus N+L and N+H have same outcome. (**d-e**) When mosquitoes are zoophilic ($p_H = 0.35$), systemic insecticides do not need to be dosed in livestock or humans as frequently as in other scenarios, due to lower rates of mosquitoes biting humans. Controlling anthropophilic mosquitoes ($p_H = 0.8$) requires an increase in dosing frequency due to the high rate of human bites. Here, m = 10. Contour definitions from left to right: weekly, monthly, quarter-annually, bi-annually, annually.

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